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Cleft Lip and Palate, Characteristic Facial Appearance, Malrotation of the Intestine, and Lethal Congenital Heart Disease in Two Sibs: A New Autosomal Recessive Condition?

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A chromosomally normal brother and sister shared a lethal pattern of anomalies including bilateral cleft lip and palate, hypertelorism, flat facial profile, flat occiput, complex congenital heart defect, and malrotation of the intestine. The male was large for gestational age, while his sister was normally grown. The girl had bifid thumbs, but the boy had only minor hand anomalies. These findings are not consistent with any previously recognized syndrome and represent a new condition with probable autosomal recessive inheritance.

KEY WORDS: autosomal recessive, cleft lip/palate, hypertelorism, congenital heart disease, malrotation

INTRODUCTION

We report a brother and sister sharing a lethal pattern of anomalies not consistent with any previously described syndrome.

CLINICAL REPORTS

Case 1

This 4,624 g (97th centile), 57 cm (>97th centile), OFC 34.5 cm (50th centile) male infant was born by forceps-assisted vaginal delivery following an uncomplicated 38-week gestation in a healthy 31-year-old mother. The Apgar scores were 1, 6, and 8 at one, 5, and 10 minutes, respectively, and he required intubation for respiratory distress. Multiple congenital anomalies were noted immediately (Fig. 1). He had a flat occiput and an unusual appearing flat face with hypertelorism (innercanthal distance 2.8 cm, >97th centile), upslanting palpebral fissures, bilateral cleft lip and palate, mild micrognathia, and bilobed tongue. The neck appeared short with mild webbing. The chest was broad with apparently wide-set nipples (chest circumference 38.5 cm, >97th centile, internipple distance 10.5 cm, >97th centile), and he had a loud systolic murmur. His abdomen was normal without mass or organomegaly. The penis was normally formed but small (length 2 cm, <3rd centile), and the left testis was not fully descended. There was a shallow sacral dimple. The limbs were of normal length with a full range of motion but the hands were short and broad with single palmar flexion creases, bilateral clinodactyly of the fifth finger, and narrow fingernails. The feet were short and broad with more notable shortness of the right fourth metatarsal. He was hypotonic with no localized neurologic abnormalities.

Karyotype was 46,XY, and X-ray films showed no major skeletal anomalies. Cardiac evaluation led to a diagnosis of hypoplastic left heart with double outlet right ventricle and pulmonic subvalvular and valvular stenosis. He died at one month, following attempted palliative surgery. Autopsy confirmed the above findings and in addition showed hepatomegaly, nephromegaly, focal endocrine hyperplasia of the pancreas, poorly fixed cecum in the right upper quadrant, and a brain with focally thinned and crowded cerebral gyri, hypoplastic poorly rotated hippocampi and subependymal, cerebellar cortical, and leptomeningeal glial heterotopias.

Case 2

This sister of case 1 was delivered by prostaglandin induction after pregnancy which had been uncomplicated until a sonogram at 16 weeks documented fetal death. Based on the clinical history and degree of maceration, she was thought to have died at about 15 weeks of gestation. Her weight of 58 g and crown-heel length of 13.8 cm were appropriate for a 15-week fetus. Externally visible anomalies included flat occiput and flat face with hypertelorism and bilateral cleft lip and palate, mild hydrops with nuchal swelling, bifid

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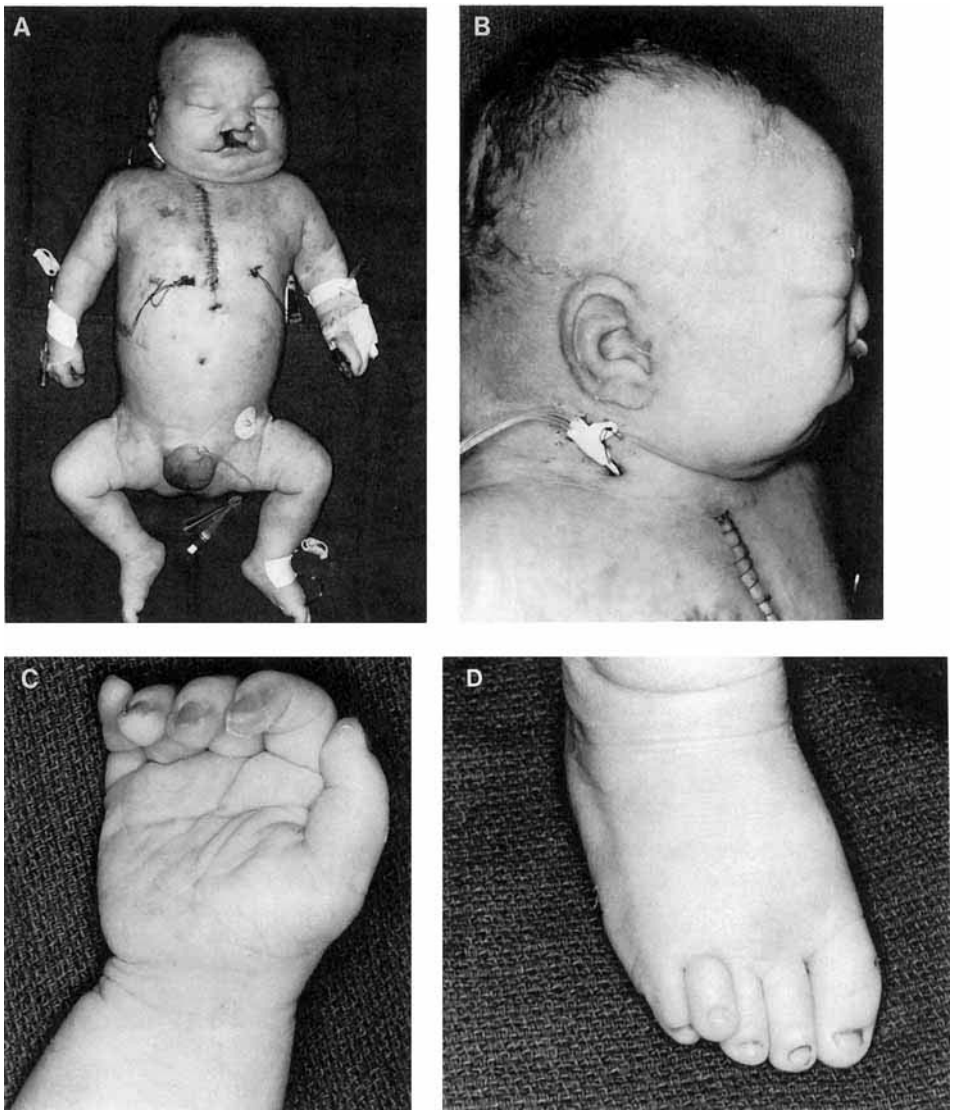

Fig. 1. **A:** Full body view of case 1 showing hypertelorism, bilateral cleft lip and palate, short neck, broad chest, and small phallus. The appearance of buried penis is due to scrotal edema which occurred terminally. The arms are of normal length, but appear short due to chest wall edema. **B:** Profile of case 1 showing flat face and occiput. **C:** Short broad hand of case 1 showing single palmar crease and narrow fingernails. **D:** Foot of case 1 showing short fourth metatarsal.

thumbs, single palmar creases, clinodactyly of the second and fifth fingers, and relatively broad feet (Fig. 2).

Karyotype was 46,XX, and X-ray studies showed no skeletal anomalies except bifid thumbs. At autopsy she was documented to have complex congenital heart disease (hypoplastic right ventricle, dysplastic pulmonary and aortic valves, ventricular septal defect (VSD), atrial septal defect (ASD), and common left pulmonary vein). The lung fissures were incomplete with normal bronchial situs. There was malrotation of the intestine with abnormal mesenteric attachments. The brain could not be studied due to maceration.

Family History

The mother and father were 33 and 35 years old, respectively, at the birth of case 2. They are healthy and nonconsanguineous. In addition to cases 1 and 2, they had an apparently healthy daughter and 2 first trimester miscarriages. Chromosomes of the parents were normal. Both parents were examined to rule out hypertelorism and microforms of cleft lip or palate, but no anomalies were found. A sib of the father was stillborn without any evidence of external anomalies. The family history was otherwise unremarkable.

DISCUSSION

Case 1 was initially thought to have Simpson-Golabi-Behmel (SGB) syndrome on the basis of macrosomia, cleft lip and palate, tongue anomaly, short broad hands, and visceromegaly with hypertrophic pancreatic islets [Golabi and Rosen, 1984]. He was recognized to be atypical for this condition due to the severity of his congen-

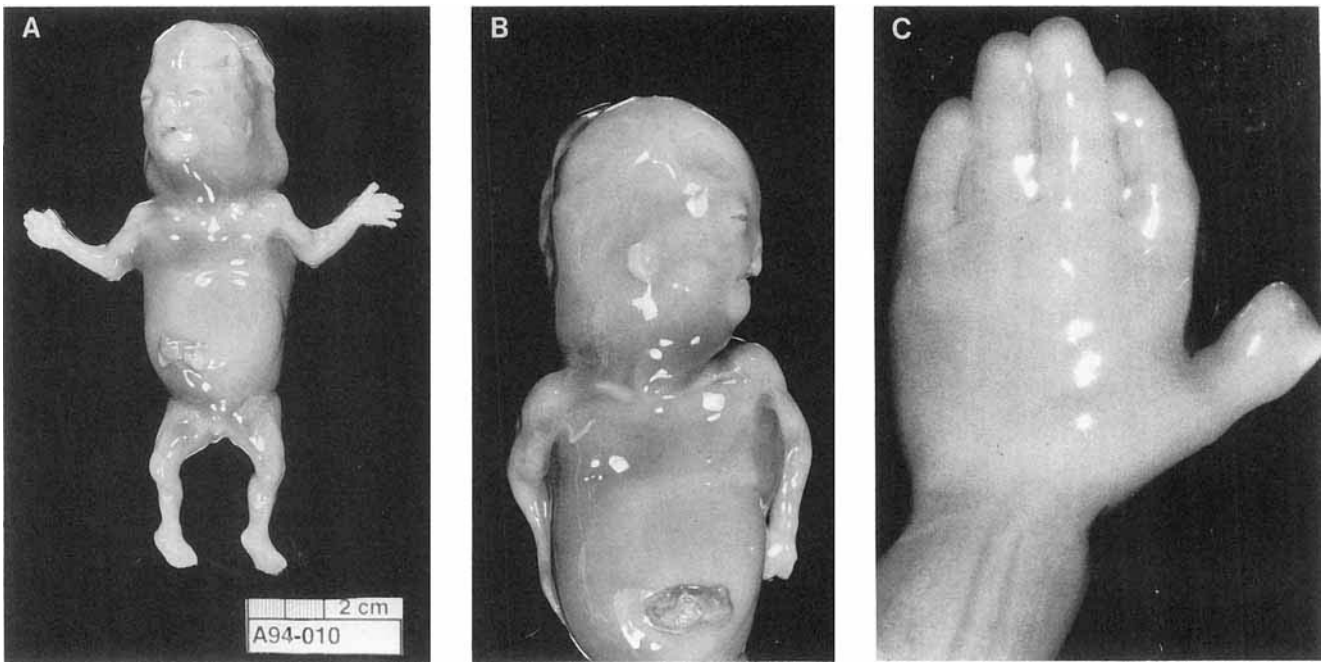

Fig. 2. **A:** Full body view of case 2 showing hypertelorism, bilateral cleft lip and palate, nuchal edema, broad chest, and bifid thumbs. The arms are of normal length but appear short due to chest wall edema. **B:** Profile of case 2 showing flat face and occiput. **C:** Hand of case 2 showing bifid thumb, single palmar crease, and clinodactyly.

ital heart defect and central nervous system anomalies. The mother shows no signs suggestive of the SGB syndrome, but since she has no brothers or maternal uncles, the family history was of limited help.

After the birth of the severely affected sister, SGB syndrome seems unlikely. Although the gene for SGB syndrome has been mapped, no specific mutations are known, and direct confirmation or exclusion of this condition is not possible [Hughes-Benzie et al., 1992]. X-inactivation studies of the female patient are pending. The occurrence of a very similar pattern of lethal anomalies in both male and female offspring of healthy parents is strongly suggestive of autosomal recessive inheritance, but no specific syndrome has been recognized. The anomalies of the face and hands in both patients as well as the macrosomia in case 1 are suggestive of Fryns syndrome but since diaphragmatic hernia is found in over 90% of patients with Fryns syndrome, yet not in either case 1 or 2, this diagnosis seems unlikely [Ayme et al., 1989]. Robinow syndrome was also considered, but neither patient has hemivertebrae or short arms by X-ray evaluation. The appearance of short arms in the accompanying figures is due to edema of the trunk in both patients. Also, the severity of the heart defects is atypical for Robinow syndrome [Bain et al., 1986]. The parents were counselled that autosomal recessive inheritance is likely and a subsequent pregnancy monitored by ultrasound resulted in the birth of a healthy daughter.

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